Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Treatment Duration and Cessation in Newly Diagnosed Multiple Myeloma (NDMM)

MASTER trial

Luciano J. Costa¹, Saurabh Chhabra², Eva Medvedova³, Bhagirathbhai Dholaria⁴, Timothy Schmidt⁵, Rebecca Silbermann³, Kelly Godby¹, Binod Dhakal², Susan Bal¹, Smith Giri¹, Aric Hall⁵, Anita D’Souza², Robert F. Cornell⁴, Pamela Hardwick¹, James Omel⁶, Parameswaran Hari², Natalie S. Callander⁵.

¹- University of Alabama at Birmingham; 2- Medical College of Wisconsin; 3- Oregon Health and Science University; 4- Vanderbilt University; 5- University of Wisconsin at Madison; 6- Independent Patient Advocate

18th International Myeloma Workshop, Vienna 2021
Disclosures

- Research support: Amgen, Janssen, BMS, AbbVie, Ionis, Genentech
- Honorarium: Amgen, Janssen, Sanofi, Karyopharm, BMS, Astra Zeneca
Background

- Daratumumab when added to PI, IMiD or PI+ IMiD combinations increases the depth and duration of responses in NDMM, including patients treated with AHCT.

- While responses are heterogeneous, treatments are typically developed without accounting for kinetics or depth of response.

- MRD is prognostic, but response-adapted therapy to achieve MRD (-) status has not been formally tested.

- Natural history of patients with confirmed MRD (-) responses managed without maintenance has not been described.
Objectives

Primary
• To determine the rate of MRD(-) responses (<10^{-5}) utilizing NGS (clonoSEQ®) in patients treated with Dara-KRd induction, AHCT, and MRD-based response-adapted Dara-KRd consolidation.

Key Secondary
• Determine the toxicity of Dara-KRd
• Determine conventional IMWG response
• Outcomes of observation without maintenance upon confirmed MRD (-)

Exploratory
• Determine MRD (-) rates by NGS with threshold of 10^{-6}

MRD tested on "first pull" and reported utilizing intent-to-treat principle according to International Harmonization
Key Eligibility

- NDMM with measurable disease
- Untreated (up to 1 cycle of VCD allowed)
- No age limit
- ECOG 0-2
- CrCl \( \geq 40 \) ml/min
- No significant cardiopulmonary disease, concomitant or recent malignancy

Planned Enrichment for MM with High-Risk Cytogenetic Abnormalities
Dara-KRd

- Daratumumab 16 mg/m² days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22

**Treatment**

**Induction**
- Dara-KRd x 4

**AHCT**

**Consolidation**
- Dara-KRd x 4

**Consolidation**
- Dara-KRd x 4

**Maintenance**
- Lenalidomide

**MRD**

- 2nd MRD (-) (<10⁻⁵)
- 2nd MRD (-) (<10⁻⁵)
- 2nd MRD (-) (<10⁻⁵)

**"MRD-SURE"** -Treatment-free observation and MRD surveillance*

*24 and 72 weeks after completion of therapy

MASTER trial
Patients

- 123 patients enrolled
- 118 (96%) with MRD trackable by ClonoSEQ®
- Median follow-up of 23.8 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard-risk</th>
<th>High-risk</th>
<th>Ultra high-risk</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 HRCA N=53 (43%)</td>
<td>1 HRCA N=46 (37%)</td>
<td>2+ HRCA N=24 (20%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (62%)</td>
<td>24 (52%)</td>
<td>13 (54%)</td>
<td>70 (57%)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (38%)</td>
<td>22 (48%)</td>
<td>11 (46%)</td>
<td>53 (43%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>60 (36-79)</td>
<td>61 (35-77)</td>
<td>60 (41-72)</td>
<td>60 (35-79)</td>
</tr>
<tr>
<td>Age ≥ 70</td>
<td>12 (23%)</td>
<td>10 (22%)</td>
<td>2 (8%)</td>
<td>24 (20%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>42 (79%)</td>
<td>33 (72%)</td>
<td>19 (79%)</td>
<td>94 (76%)</td>
</tr>
<tr>
<td>Racial/ethnic minorities</td>
<td>11 (21%)</td>
<td>13 (28%)</td>
<td>5 (21%)</td>
<td>29 (23%)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>42 (79%)</td>
<td>40 (87%)</td>
<td>17 (71%)</td>
<td>99 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>11 (21%)</td>
<td>6 (13%)</td>
<td>7 (29%)</td>
<td>24 (20%)</td>
</tr>
</tbody>
</table>

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial
### Patients (cont)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard-risk 0 HRCA</th>
<th>High-risk 1 HRCA</th>
<th>Ultra high-risk 2+ HRCA</th>
<th>Total N=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;ULN</td>
<td>45 (85%)</td>
<td>34 (74%)</td>
<td>18 (75%)</td>
<td>97 (79%)</td>
</tr>
<tr>
<td>≥ ULN</td>
<td>8 (15%)</td>
<td>12 (26%)</td>
<td>6 (25%)</td>
<td>26 (21%)</td>
</tr>
<tr>
<td>Cytogenetic abnormality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperdiploidy</td>
<td>27 (51%)</td>
<td>20 (44%)</td>
<td>4 (17%)</td>
<td>51 (41%)</td>
</tr>
<tr>
<td>del(13q)</td>
<td>19 (36%)</td>
<td>20 (44%)</td>
<td>18 (75%)</td>
<td>57 (46%)</td>
</tr>
<tr>
<td>gain/amplification 1q</td>
<td>0 (0%)</td>
<td>24 (52%)</td>
<td>20 (83%)</td>
<td>44 (36%)</td>
</tr>
<tr>
<td>del(1p)</td>
<td>3 (6%)</td>
<td>4 (9%)</td>
<td>5 (21%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>14 (26%)</td>
<td>7 (15%)</td>
<td>0 (0%)</td>
<td>21 (17%)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>0 (0%)</td>
<td>8 (17%)</td>
<td>13 (54%)</td>
<td>21 (17%)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>4 (17%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>0 (0%)</td>
<td>12 (26%)</td>
<td>14 (58%)</td>
<td>26 (21%)</td>
</tr>
<tr>
<td>R-ISS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25 (47%)</td>
<td>11 (24%)</td>
<td>0 (0%)</td>
<td>35 (28%)</td>
</tr>
<tr>
<td>2</td>
<td>27 (51%)</td>
<td>23 (50%)</td>
<td>13 (54%)</td>
<td>63 (51%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (2%)</td>
<td>12 (26%)</td>
<td>11 (46%)</td>
<td>25 (20%)</td>
</tr>
</tbody>
</table>

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)
Safety

Any Grade | Grade ≥ 3
---|---
Any | 123 (100) | 91 (74)

**Hematologic**

| Adverse Event | No. of patients | (%)
|---|---|---|
| Neutropenia | 51 (41) | 43 (35)
| Lymphopenia | 34 (28) | 27 (22)
| Anemia | 26 (21) | 13 (11)
| Thrombocytopenia | 24 (20) | 10 (8)
| Leukopenia | 22 (18) | 12 (10)

**Non-Hematologic**

| Adverse Event | No. of patients | (%)
|---|---|---|
| Fatigue | 68 (55) | 11 (9)
| Bone pain | 68 (55) | 7 (6)
| Rash maculo-papular | 50 (41) | 5 (4)
| Nausea | 49 (40) | 0
| Constipation | 48 (39) | 0
| Upper Respiratory Infection | 45 (37) | 1 (1)
| Diarrhea | 43 (35) | 5 (4)
| Insomnia | 35 (28) | 3 (2)
| Infusion related reaction | 34 (28) | 2 (2)
| Dyspnea | 34 (28) | 2 (2)
| Cough | 32 (26) | 0
| Hypertension | 32 (26) | 12 (10)
| Dizziness | 30 (24) | 1 (1)
| Peripheral sensory neuropathy | 26 (21) | 2 (2)

- 25 TE-SAEs
  - Pneumonia (N=8)
  - Pulmonary embolism (N=3)
  - Fever and neutropenia (N=2)
  - aHUS (N=1)
  - IRR (N=1)
  - Atrial fibrillation (N=1)
  - Other (N=9)

- 3 deaths
  - Unwitnessed sudden death on second week of induction
  - Metapneumovirus pneumonia 9 days after AHCT
  - Unwitnessed sudden death 2 months after AHCT
Best MRD response by phase of therapy

**NSG MRD < 10^{-5}
Primary endpoint**
- All Patients
  - Post Induction (N=118)
  - Post-AHCT (N=118)
  - MRD-directed consolidation (N=118)
- 0 HRCA
  - Post Induction (N=50)
  - Post-AHCT (N=50)
  - MRD-directed consolidation (N=50)
- 1 HRCA
  - Post Induction (N=44)
  - Post-AHCT (N=44)
  - MRD-directed consolidation (N=44)
- 2+ HRCA
  - Post Induction (N=24)
  - Post-AHCT (N=24)
  - MRD-directed consolidation (N=24)

**NGS MRD < 10^{-6}
Exploratory endpoint**
- All Patients
  - Post Induction (N=118)
  - Post-AHCT (N=118)
  - MRD-directed consolidation (N=118)
- 0 HRCA
  - Post Induction (N=50)
  - Post-AHCT (N=50)
  - MRD-directed consolidation (N=50)
- 1 HRCA
  - Post Induction (N=44)
  - Post-AHCT (N=44)
  - MRD-directed consolidation (N=44)
- 2+ HRCA
  - Post Induction (N=24)
  - Post-AHCT (N=24)
  - MRD-directed consolidation (N=24)

**HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)**
MRD level by phase of therapy

0 HRCA

62% confirmed <10^{-5}

Treatment cessation

1 HRCA

78% confirmed <10^{-5}

Treatment cessation

2+ HRCA

63% confirmed <10^{-5}

Treatment cessation

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)
Best IMWG response by phase of therapy

- 6 progressions during therapy
  - 1 during induction,
  - 1 after AHCT
  - 4 on consolidation
- All with gain/amp of 1q
- 5/6 had 2+ HRCA

Post Induction Cycle 2 (N=123):
- SD: 36%
- PR: 10%
- VGPR: 52%
- CR: 1%
- sCR: 3%

Post Induction Cycle 4 (N=123):
- SD: 63%
- PR: 33%
- VGPR: 3%
- CR: 67%
- sCR: 3%

Post Transplant (N=123):
- SD: 36%
- PR: 25%
- VGPR: 2%
- CR: 89%
- sCR: 2%

MRD-based consolidation (N=123):
- SD: 33%
- PR: 67%
- VGPR: 3%
- CR: 84%
- sCR: 2%

MASTER trial
Conclusions

- NGS MRD-based, response adapted therapy is feasible in ~96% of patients in multi center setting.

- Dara-KRd is a safe regimen with rapid responses and unprecedented rates of MRD negativity in NDMM achievable across the risk spectrum

- Quadruplet therapy and achievement of confirmed MRD (-) CR enables the exploration of treatment cessation and “MRD-SURE” as alternative to continuous therapy.

- Novel consolidative strategies need to be explored in ultra high-risk patients with suboptimal clearance of MRD on quadruplet therapy

Long term follow up will inform the risk of progression and MRD resurgence during MRD-SURE

MASTER trial
**Future**

**Induction**
- Quadruplet x 6 cycles
  - MRD1 < 10^-5
    - Arm A
    - MRD (-) randomization
    - AHCT
  - MRD1 ≥ 10^-5
    - Arm B
    - MRD (+) randomization
    - AHCT
- Stem cell collection

**Intensification**
- Quadruplet X 3 cycles
  - MRD1 < 10^-5
    - Arm A
    - MRD (-) randomization
    - AHCT
  - MRD1 ≥ 10^-5
    - Arm B
    - MRD (+) randomization
    - AHCT

**Consolidation**
- T-cell Redirecting therapy
  - MRD (-) randomization
  - AHCT
  - CD38MoAb-R x 3 cycles
  - MRD1x

**Maintenance**
- CD38MoAb-R x 1 year
  - MRD2
- Dara-R x 1 year
  - MRD3
- T-cell Redirecting therapy
  - MRD2
- CD38MoAb-R x 1 year
  - MRD3

**Sustained MRD Negativity**
- Otherwise SOC maintenance

**MRD-SURE**
- Treatment-free observation and MRD surveillance

*MRD-SURE – Treatment-free observation and MRD surveillance*
Acknowledgements

- Patients and their families.
- Performed by Academic Consortium to Overcome Multiple Myeloma through Innovative Trials (COMMIT)
- James Omel and Yelak Biru
- Investigator-initiated trial, support from Amgen and Janssen.
- Adaptive Biotechnologies for partnership and assistance with IDE

- Clio Wang
- Tiffany Hill
- Yvonne Duke
- Liz Busby
- Megan Bouillon
- Melisa Sentell
- Evan Hudson
- Lesley Miller

- Mathew Ware
- Sarah Ramirez
- Catharine Skoog
- Deepa Pereira
- Taylor Keaton
- Megan Offolter
- Sara Leonard
- Paulette Jacobs

- Amber Boyce
- Chris Seybold
- Nicholas Anderson
- Rachel W Smith
- Daniel White

- Carina Knoespel
- Christopher D'Angelo
- Carolyn Serpe
- Mitch Howard

- Deborah Sutherland
- Sahar Vali
- Kyle Rawling